DIASTEREOSELECTIVE SYNTHESIS OF BRIDGEHEAD HETEROBICYCLIC SPIRO COMPOUNDS DERIVED FROM TANDEM MICHAEL INTRAMOLECULAR 1,3-DIPOLAR CYCLOADDITION OF NITRONES

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Abstract

The reaction of cyclic oximes with divinyl sulfone afforded bridgehead heterobicyclic spiro compounds in good yields. The formation of diastereomerically single systems involved conjugate addition of oxime onto the diene sulfone to give transient N-alkenylnitrones that then underwent subsequent intramolecular dipolar cycloaddition reaction. The diastereoselectivity of the process was predicted by MOPAC AM1 calculations.

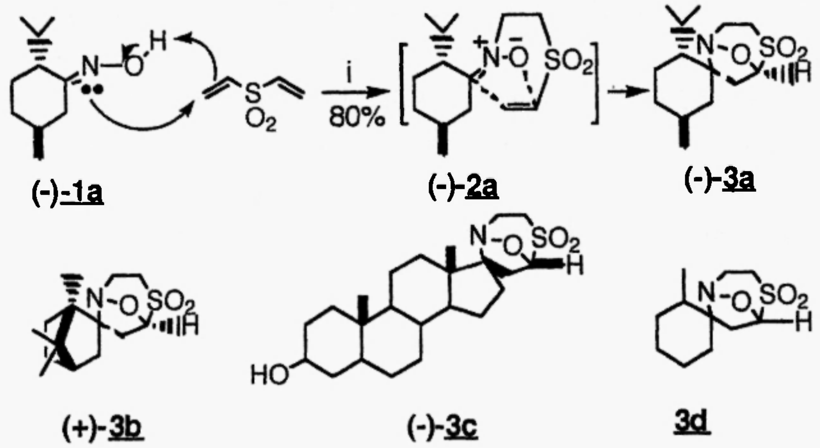
Introduction

Tandem reactions have emerged in recent years as a powerful means for their operational simplicity and frequently observed selectivity, providing an impetus momentum in organic synthesis (1). Prominents in this field are Michael initiated reactions, followed by a facial intramolecular cycloaddition (2), which has a great deal of importance specially for preparing highly functionalized nitrogen heterocycles (3). In addition, oximino dienophiles such as oximes or oxime ethers are of considerable interest because of their potential values in natural product synthesis (4). Recently a number of groups have developed a good number of methods for the generation of N-alkenylnitrones involving mainly an oxime interacted with an activated π-bond (5). Its basic sequence was first examined by Ochiai and his co-workers in 1967 (6) and which have been nicely exploited by Padwa (7), Grigg (8), Hassner (9) and others (10,11), over the past several years.

As a part of our ongoing interest in nitrone cycloaddition chemistry (12), we thought that its worthwhile to investigate the scope of quantitatively functionalized N-alkenyl nitrone cycloaddition and to isolate the resulting selectively fashioned bridgehead heterobicyclic spiro compounds. This report out lines our successful achievement of this target.

Results and Discussion

The chiral N-linked alkenylnitrones were generated *in situ* from the reactions of chiral oximes such as (-)-menthone oxime, (+)-camphor oxime, epiandrosterone oxime with divinyl sulfone in boiling toluene and cyclized in the same conditions to afford diastereomerically pure bridgehead heterobicyclic spiro compounds **3a-c**(13) in good yields (**Scheme 1**, **Table 1**). The structural



Reagents and Conditions : i) Toluene, reflux, 20-30h
Scheme 1

Table 1. Diastereoselective synthesis of bridgehead type compounds **3**.

Product	Oximes	Yield (%)	$[\alpha]_D^{26}$ c=1.0,$CHCl_3$	*de*[a] (%)
(-)-**3a**	(-)-**1a**	80	-66.032	>96[b]
(+)-**3b**	(+)-**1b**	74	+90.725[c]	>96[b]
(-)-**3c**	(-)-**1c**	67	-0.6934	>96[b]
3d	**1d**	66	d	d

[a] The *de* values were determined by ^{1}H NMR spectroscopy (Bruker DRX 400MHz spectrometer).
[b] In ^{1}H NMR spectrum there were no peaks corresponding to the other isomers.
[c] Measured at 27°C. [d] The data were not determined.

assignments of all the bridgehead systems were ascertained by IR, ^{1}H & ^{13}C-NMR, DEPT, HMQC and HRMS. These informations were further confirmed by a single crystal X-ray analysis (**Figure 1**)(14). Here its clear that the orientation of substituents, specially the presence and the nature of

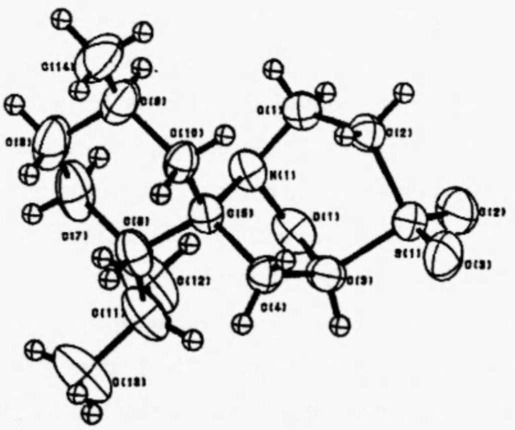
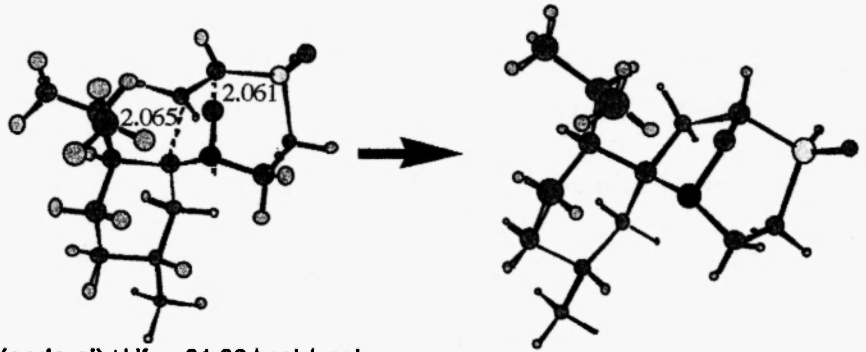
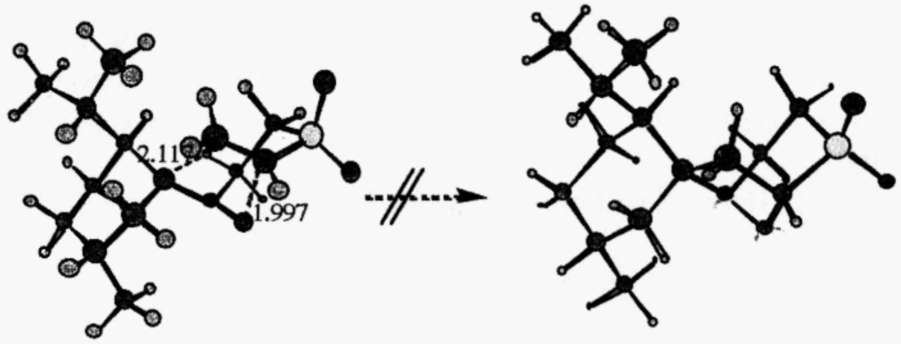


Figure 1. ORTEP drawing of (-)-**3a**

substituents located at α-to nitrone function and the geometry of the parent cyclic system can effectively control the regiochemistry, as well as the stereochemistry of the cycloaddition process. We are pleased to observe the formation of desired cycloadducts under one-pot condition by adapting the procedure of Frederickson et al (11) with slight modifications. In addition the transition energy calculated by AM1



TS-1(endo-si) ΔHf = -31.38 kcal / mol



TS-2(exo-re) ΔHf = -24.60 kcal / mol

Figure 2. Transition state(TS) energies calculated by MOPAC AM1

is consistent with the observed experimental results. Accordingly the heat of formation of **endo-si** (**TS-1**, ΔHf -31.38 kcal/mol) is less by 6.78 kcal/mol than that of **exo-re** (**TS-2**, ΔHf -24.60 kcal/mol (**Figure 2**), large enough to control the process for producing a single diastereomer. Actually the regiochemistry of the nitrone intramolecular dipolar cycloaddition reaction is complicated by a complex interplay of factor, such as alkene polarity, ring strain and other nonbonded interactions (7). In the similar works of Grigg (15) and Padwa (4, 7) a significant loss of regioselectivity was observed. Many groups (16-18) have investigated the basic rule and nature of 1,3-dipolar cycloaddition and their results were in good agreement with the concerted mechanism. In present study, the interatomic distances of involved atoms at **TS-1** were 2.061Å for C-O and 2.065Å for C-C and their difference is 0.004Å, which agreed the concerted pathway.

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(13) **Preparation of compounds 3; General procedure**
A solution of oximes (19) **1a-d** (7.45 mmol) and divinyl sulfone (7.45 mmol) in toluene (150 ml) was refluxed for 20-30 h. After cooling the solvent was removed *in vacuo* and the residue was recrystallized from ethyl acetate and hexane solution (3:1) to give single regioisomers **3a-d** (66-80%) (**Table 1**), which were then subjected to be analyzed for the determination of the

structure and the stereochemistry

Cycloadduct (-)-3a

Pale yellow plates (80%); mp 260-261℃; IR(KBr) v=2950, 2875, 1460, 1430, 1420, 1360, 1300, 1380, 1220, 1160, 1140, 1120, 1060, 1020, 950, 930, 860, 810, 750 cm-1. ^{1}HNMR (400MHz, $CDCl_3$/TMS) δ= 0.82-1.05(m, 3H, 3H, 3H, 1H, 1H), 1.50-1.58(m, 1H, 1H), 1.63-1.67(m, 1H), 1.78-1.81(m, 1H, 1H), 2.40(dd, 1H, J = 4.0, 4.0Hz), 2.80(dd, 1H, J = 8.0, 8.0Hz), 3.09-3.12(m, 1H), 3.36-3.39(m, 1H), 3.44-3.46(m, 1H), 3.98-4.04(m, 1H), 4.83-4.86(m, 1H) . ^{13}C NMR (100.62 MHz, $CDCl_3$) δ= 17.83(CH_3), 2.52(CH_3), 22.83(CH_2), 24.79(CH_3), 27.41(CH), 30.55(CH), 35.04(CH_2), 43.69(CH_2), 43.79(CH_2), 46.31(CH_2), 48.43(CH_2), 53.55(CH), 71.52(C), 90.71(CH). HRMS (FAB), m/z, (M+1): calcd for $C_{14}H_{26}NO_3S$ 288.1633, found 288.1642.

(14) Details of the crystal structure determination are available on request from Cambridge Crystallographic Data Centre; CCDC 139319 for the compound **(-)-3a**.

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